

# VIRAL RESPIRATORY ILLNESSES OF INFANTS AND CHILDREN<sup>1</sup>

HENRY G. CRAMBLETT

*Department of Pediatrics, Ohio State University, and Children's Hospital, Columbus, Ohio*

INTRODUCTION.....	431
PROBLEMS IN THE ETIOLOGICAL STUDY OF VIRAL RESPIRATORY ILLNESS IN INFANTS AND CHILDREN	431
CLINICALLY INDISTINGUISHABLE RESPIRATORY ILLNESSES.....	433
<i>Rhinitis</i> .....	433
<i>Tonsillitis or Pharyngitis</i> .....	433
<i>Exanthematous Disease</i> .....	434
<i>Laryngitis</i> .....	434
<i>Bronchitis</i> .....	435
<i>Pneumonia</i> .....	435
<i>Bronchiolitis</i> .....	435
CLINICALLY DISTINGUISHABLE RESPIRATORY ILLNESSES.....	436
<i>Influenza</i> .....	436
<i>Herpangina</i> .....	437
SUMMARY.....	437
LITERATURE CITED.....	437

## INTRODUCTION

During recent years, advances in virological methodology have enabled investigators to pursue studies which have delineated the extent to which a number of viruses are capable of causing respiratory disease in infants and children. The present discussion will summarize briefly certain problems in such etiological studies and outline present knowledge of the part viruses play in respiratory illnesses in infants and children. In addition, the characteristics of an apparently "new" virus (respirolyticvirus) recovered from children with respiratory illnesses during the period February through April, 1964, will be discussed.

## PROBLEMS IN THE ETIOLOGICAL STUDY OF VIRAL RESPIRATORY ILLNESS IN INFANTS AND CHILDREN

The association of infection with a virus and respiratory illness in infants and children is often difficult to establish. In any longitudinal study in which well children are cultured as controls, or in which infants and children are cultured without respect to presence or absence of illness, a viral excretion rate will be established which is related

most closely to the age of the subject studied. For instance, in a recent study of infants under 6 months of age attending a well-baby clinic, 55% of all virus isolations were from infants who had no respiratory illness (11). Conversely, viruses were recovered from fewer than 25% of the infants who actually had respiratory illnesses. Overall, from 13 to 19% were excreting virus. For comparison, a group of 268 children 5 to 18 years of age, who made 1,388 visits to a rheumatic fever clinic, were studied for rate of virus excretion without regard to presence or absence of acute illness. It was found that the virus excretion rate in these children was 3.8%. A possible explanation for the higher virus excretion rate in infants less than 6 months of age is that, as their passively transferred immunity wanes, they become subject to infection with a multitude of viruses. Although inadequate to prevent infection, enough passively transferred immunity remains to prevent serious illness in most instances. In addition to virus excretion by well children, longitudinal studies are also made more difficult by the fact that a given infant or child with respiratory illness may be harboring more than one potential pathogen, either viral or bacterial, at the time of observation (5, 22).

The spectrum of illness that a given virus or group of viruses may cause in infants and children is broad. To illustrate, adenoviruses are generally accepted as causing 5 to 9% of all

<sup>1</sup> A contribution to the Symposium on "Current Progress in Virus Diseases" presented as part of the program for the Centennial of the Boston City Hospital, 1 June 1964, with Maxwell Finland serving as Consultant Editor, and John H. Dingle and Herbert R. Morgan as moderators.

respiratory illnesses (7, 16). The anatomic respiratory syndromes caused by the adenoviruses are diverse. In Table 1 are listed the diseases in patients from whom adenoviruses were recovered in our laboratory in the past 36 months. During the course of this study, infants and their mothers in a well-baby clinic, hospitalized infants and children, children in a children's home (12), and patients in a rheumatic fever clinic were studied for excretion of viruses. Although the simultaneous presence of other viral and bacterial pathogens was excluded in this study, and study

TABLE 1. *Illnesses in patients excreting adenoviruses*

Disease	No. of patients
Rhinitis.....	25
Pharyngitis	
Severe.....	9
Moderate.....	7
Mild.....	2
Conjunctivitis.....	3*
Laryngitis (croup).....	2*
Bronchitis.....	1
Pneumonia.....	5
Bronchiolitis.....	1
Undifferentiated febrile illness.....	7
Gastroenteritis.....	4
Guillain-Barre syndrome.....	2
Well.....	17
Total.....	85

\* One patient in each of these categories had a dual infection with two adenoviruses.

of the patients' sera revealed an appropriate antibody response, evidence was not sufficient in all cases to prove that the adenoviruses recovered played an etiological role in the patients' illnesses. It is also pertinent to stress that 20% of the viruses were from well patients. Of the 85 adenoviruses recovered, 39 (46%) were from infants 6 months of age or less. Of the 17 viruses recovered from well patients, 13 (76%) were from infants less than 6 months of age. The number of each type of adenovirus recovered is listed in Table 2 and, in general, reflects the serotypes most likely to be recovered in studies of infants and children. Data relating to recovery of parainfluenza viruses are listed in Table 3. Again, it is evident that these viruses may cause a broad spectrum of respiratory illnesses and also that they may be recovered from well children.

Not only must one be aware that each virus may cause a broad spectrum of illness in the initial infection, but there is increasing evidence that certain viruses may cause recurrent or secondary infections and illnesses. In general, as for example with parainfluenza viruses or respiratory syncytial virus, the illness associated

TABLE 2. *Number of each type of adenovirus recovered*

Adenovirus type	No. of patients
1	23*
2	25
3	26*
4	1
5	5
6	1
7	1
9	1*
12	4
Total	87

\* Two patients were simultaneously excreting adenovirus types 1 and 3 and types 3 and 9.

TABLE 3. *Illnesses associated with parainfluenza (types 1, 2, and 3) infections*

Disease	No. of patients	Per cent
Rhinitis.....	15	30
Croup.....	14	28
Undifferentiated febrile illness.....	8	16
Pharyngitis		
Moderate.....	1	
Mild.....	5	12
Bronchitis.....	1	2
Bronchopneumonia.....	1	2
Well.....	5	10
Total.....	50	100

with the initial infection in the infant or young child is frequently severe and tends to involve the lower respiratory tract, whereas the illness accompanying the recurrent infection may be a mild upper respiratory one (2, 15).

In the present discussion, emphasis will be given to the importance of various viruses in the etiology of certain anatomic syndromes in infants and children. Available statistics of the frequency with which viruses cause certain syndromes may be misleading. None of the studies to be quoted

includes data utilizing concurrently all of the present virological techniques over a sufficiently long period to give a representative picture of the importance of all viruses. As each new virus or group of viruses capable of causing respiratory disease is described, it becomes necessary to re-evaluate all viruses in similar terms in similar studies, with the use of methods that will recover as many pathogens as possible. Further, the data from any single study are compromised because the importance of any virus or group of viruses in the etiology of respiratory disease will vary from season to season, from year to year, and from geographic area to geographic area (4).

#### CLINICALLY INDISTINGUISHABLE RESPIRATORY ILLNESSES

Since the infant or young child is unable to offer complaints, it is helpful etiologically to the pediatrician to consider respiratory illnesses from the standpoint of the anatomic portion of the respiratory tract in which there is initial maximal involvement. Such a classification is likely to be somewhat artificial, since more than one portion of the respiratory tract of a patient may become involved during the course of a viral infection. The following discussion is based on the initial and most prominent early involvement and will summarize the current knowledge of the viral etiology of rhinitis, tonsillitis or pharyngitis, croup, bronchitis, pneumonia, and bronchiolitis in infants and children.

##### *Rhinitis*

As an anatomic syndrome, rhinitis includes those illnesses in which nasal congestion, rhinorrhea, and sneezing are prominent early symptoms. Fever is more often present in infants and children than in adults. Cough may occur later but is not prominent initially. Sore throat (or pharyngeal erythema) may be present but is not a major complaint. Other terms used to describe this syndrome include "ARD," "URI," "common cold," and "coryza."

Rhinitis may be due to any one of a large number of viruses which usually cause more dramatic respiratory illnesses. Among these viruses are included the adenoviruses, Coxsackie viruses, influenza viruses, parainfluenza viruses, and respiratory syncytial virus. The overall importance of the rhinoviruses as a cause of the syndrome in infants and children has not yet been fully assessed. Our studies to date would indicate

that rhinoviruses are an important cause of rhinitis, but it is doubtful that they will be found to be as prevalent in children as in adults. In contrast to their action in adults, it seems that these viruses are more likely to cause fever and lower respiratory tract involvement in infants and children (19).

In our own studies of respiratory illnesses, both longitudinally in a children's home and in hospitalized patients, parainfluenza viruses and adenoviruses have been frequently recovered from patients with this syndrome (Tables 1 and 3); 29% of adenoviruses and 30% of parainfluenza viruses recovered have been from patients in whom the diagnosis of rhinitis was made, and fever was present in all. During outbreaks of influenza A and B, the diagnosis of rhinitis was made in many patients who subsequently proved virologically to have influenzal infections (10).

##### *Tonsillitis or Pharyngitis*

In attempting to ascertain the etiology of tonsillitis or pharyngitis, it is helpful to the clinician to use certain criteria which statistically will help differentiate the illnesses due to viruses from those due to group A  $\beta$ -hemolytic streptococci. In our experience studying children (5 to 18 years of age) in a children's home, it has been helpful to divide pharyngitis into severe, moderate, and mild categories (12).

Severe pharyngitis, in which there is unequivocal fever, exudate, and erythema of the tonsillar areas, is due in 88% of cases to group A  $\beta$ -hemolytic streptococci. The remainder may be due to viruses and, in our experience, groups A and B Coxsackie viruses, adenoviruses, and influenza viruses have been most frequently recovered (Table 1) (10, 12).

Moderate pharyngitis, in which there are present two of the three characteristics of fever, exudate, and pharyngeal erythema, is due in about 50% of cases to group A  $\beta$ -hemolytic streptococci. In the remainder of cases, either a virus may be ascribed an etiological role, or no pathogen is recovered. Among the viruses which have been recovered from such patients are the Coxsackie viruses, adenoviruses, parainfluenza viruses, influenza viruses, and ECHO viruses (Tables 1 and 3) (10, 12, 14). The role of the rhinoviruses, respiratory syncytial virus, and reoviruses in causing primary tonsillitis or pharyngitis has not yet been delineated.

In patients with mild pharyngitis, i.e., sore

throat or mild pharyngeal erythema without fever or exudate, 78% or more are due to viruses. Probably any and all of the respiratory viruses and some of the enteroviruses may cause this syndrome.

#### *Exanthematous Disease*

Frequently, as depicted in Fig. 1, an upper respiratory illness may occur as the initial part of a biphasic illness. The major manifestation of the biphasic illness may take one of several forms, such as an exanthem.

The classical viral exanthematous disease in which there are prominent preceding upper respiratory signs and symptoms is rubeola. How-

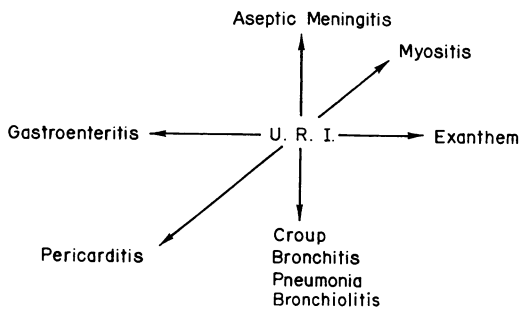


FIG. 1. Schematic representation of biphasic viral illnesses in which the initial disease is an upper respiratory illness.

ever, in the past 15 years a large number of viruses have been recovered, mostly from children with exanthems who also have had sore throat, coryza, or other manifestations of upper respiratory tract involvement (8). Although the association between infection with these viruses and illnesses observed has not been proven in all cases, the available evidence is highly suggestive of such an association. The viruses involved include Coxsackie group A viruses, types 2, 4, 9, and 16; Coxsackie group B viruses, types 1, 3, and 5; ECHO virus, types 2, 3, 4, 5, 6, 9, 11, 14, 16, 18, and 19; reovirus, type 2; and adenovirus, types 1, 2, and 3.

#### *Laryngitis*

Croup is a syndrome with inspiratory stridor, cough, and hoarseness, due to varying degrees of laryngeal obstruction, and is one of the commonest respiratory illnesses prompting an "emergency" call to the physician. For the purposes of etiological discussion, laryngitis, laryngotracheitis, and laryngotracheobronchitis

will be considered jointly, as all may be caused by the same agents. From a practical standpoint, the only reason for differentiation is for purposes of prognosis. Traditionally, most classifications of croup have included a category spoken of as "spasmodic croup." Typically, this form of croup has been described as developing suddenly at night, tending to be recurrent, and associated with minor upper respiratory infections. "Spasmodic croup" was said to be due to allergy or immaturity of the larynx and to occur in the "nervous" type of child. No doubt a major portion of the laryngeal obstruction in this form of the disease is due to spasm with a lesser degree of actual subglottic edema. However, there is increasing evidence that the laryngeal spasm is triggered by, and associated with, a preceding or concomitant upper respiratory infection in the majority of cases. Moreover, there is a greater chance that a child who has had one episode of croup will have subsequent episodes. Just why one child with a given viral infection has only minor upper respiratory signs and symptoms while another will have sudden onset of croup is unknown, but one is forced to postulate that a "croup diathesis" exists. Specimens from many children with recurrent episodes of croup have been studied, and a viral etiology (direct or indirect) has been established. As an example, one child was studied who had croup at ages 4, 11, and 29 months. The first illness was associated with infection with parainfluenza type 2 virus, the second with Asian influenza, and the third with ECHO virus type 13 infection. As an additional example, two sisters were studied who developed their initial episodes of "spasmodic" croup simultaneously at the ages of 6 and 26 months. ECHO virus type 9 was recovered from their throat and anal washings. After 4 months, they again had croup and, in both, simultaneous infection with parainfluenza type 3 virus was found. It does not seem tenable, therefore, to make a sharp distinction between "infectious croup" and "spasmodic croup," which implies that the latter is in no way related to infection (4).

Many careful studies of patients with croup have helped to delineate the statistical importance of the various pathogens in its infectious etiology. Rabe, in his careful early studies, reached the conclusion that at least 85% of patients had croup on a nonbacterial basis (18). In three different studies of the etiology of non-

bacterial croup, 36, 50, and 64% of the patients were found to be infected with various viruses (Table 4). To date, the parainfluenza viruses have been found to be the single most important group of viruses causing croup. Early reports suggested that infection with parainfluenza virus type 2 was more likely to cause croup than any other respiratory syndrome (1, 17). In our experience, however, parainfluenza type 2 virus has been associated with acute rhinitis as often as with croup.

TABLE 4. *Etiology of nonbacterial croup*

Virus	Per cent reported		
	McLean (9)	Parrott (16)	This report
Adenovirus.....	—	9	4
Influenza (A + B)....	1.5	8	6
Parainfluenza 1.....	30	21	8
Parainfluenza 2.....	0.5	8	6
Parainfluenza 3.....	4	10	14
Respiratory syncytial..	—	8	—
ECHO viruses.....	0.2	—	10
Coxsackie viruses.....	—	—	2
No virus recovered....	64	36	50

*Bronchitis*

Bronchitis is frequently associated with laryngitis, rhinitis, or tonsillitis/pharyngitis. Therefore, it is not surprising that the viruses causing these syndromes have also been found to cause bronchitis. In one study, 24% of all children with bronchitis/pharyngitis were found to have their disease due to respiratory syncytial virus (16). The parainfluenza viruses as a group were responsible for 18% of the illnesses. The rhinoviruses may cause lower respiratory disease, chiefly bronchitis, in children, in addition to rhinitis (19). Other viruses causing bronchitis in infants and children include the influenza viruses and adenoviruses.

*Pneumonia*

The various viruses that have been demonstrated to cause viral pneumonia include the measles virus, parainfluenza viruses, adenoviruses, psittacosis virus, respiratory syncytial virus, lymphocytic choriomeningitis virus, and influenza viruses A, B, and C. As in the case of bronchitis, the respiratory syncytial virus and the parainfluenza viruses are of major etiological importance.

During the period February through April,

1964, 64 recoveries of an apparently "new" virus were made in our laboratory from infants and children, many of whom had respiratory disease including rhinitis, tracheobronchitis, and pneumonia. The more severe lower respiratory illnesses occurred in infants and younger children. One child who died was found to have extensive pulmonary interstitial infiltrate at postmortem examination.

The virus was recovered on primary isolation from washings of both throat and anal swabs in a continuous cell culture of skin, but not in monkey kidney cell cultures. On passage, the virus grew in monkey kidney and WI-38 cell cultures. The cytopathic effect is distinctive, and resembles that produced by mumps virus (Fig. 2) (20). This virus, at present termed the respirolyticvirus, is pH-labile and ether-sensitive, and hemagglutinates both human group O and guinea pig erythrocytes at 4 C. The virus readily passes through a 220-mμ filter (Millipore) but does not pass through a 100 -mμ filter. Serologically, the virus is not related to mumps virus, respiratory syncytial virus, or the parainfluenza viruses.

This virus was recovered more frequently in our laboratory during the period January through May, 1964, than all other viruses combined. Further studies are underway to characterize it and to further assess its importance in the etiology of respiratory disease.

*Bronchiolitis*

Bronchiolitis is a severe illness with involvement pathologically of the lower respiratory tract and, in particular, the terminal bronchioles. There are varying degrees of interstitial infiltrate. Characteristically, bronchiolitis occurs in infants less than 9 months of age. In most instances, the infant has a preceding mild upper respiratory infection which culminates acutely in a syndrome consisting of tachypnea, dyspnea, tachycardia, signs of peripherovascular collapse, emphysema, rales, and cyanosis. The disease occurs most frequently during the winter months. The case fatality rate varies considerably from year to year and this, in itself, suggests a varied etiology.

Bronchiolitis has been thought to be viral in origin for many years, because no consistent bacterial pathogen has ever been recovered from these patients. Several studies have shown that the respiratory syncytial virus is a major cause of this syndrome and that, in some instances, parainfluenza viruses and adenoviruses may be assigned an etiological role (2, 16).

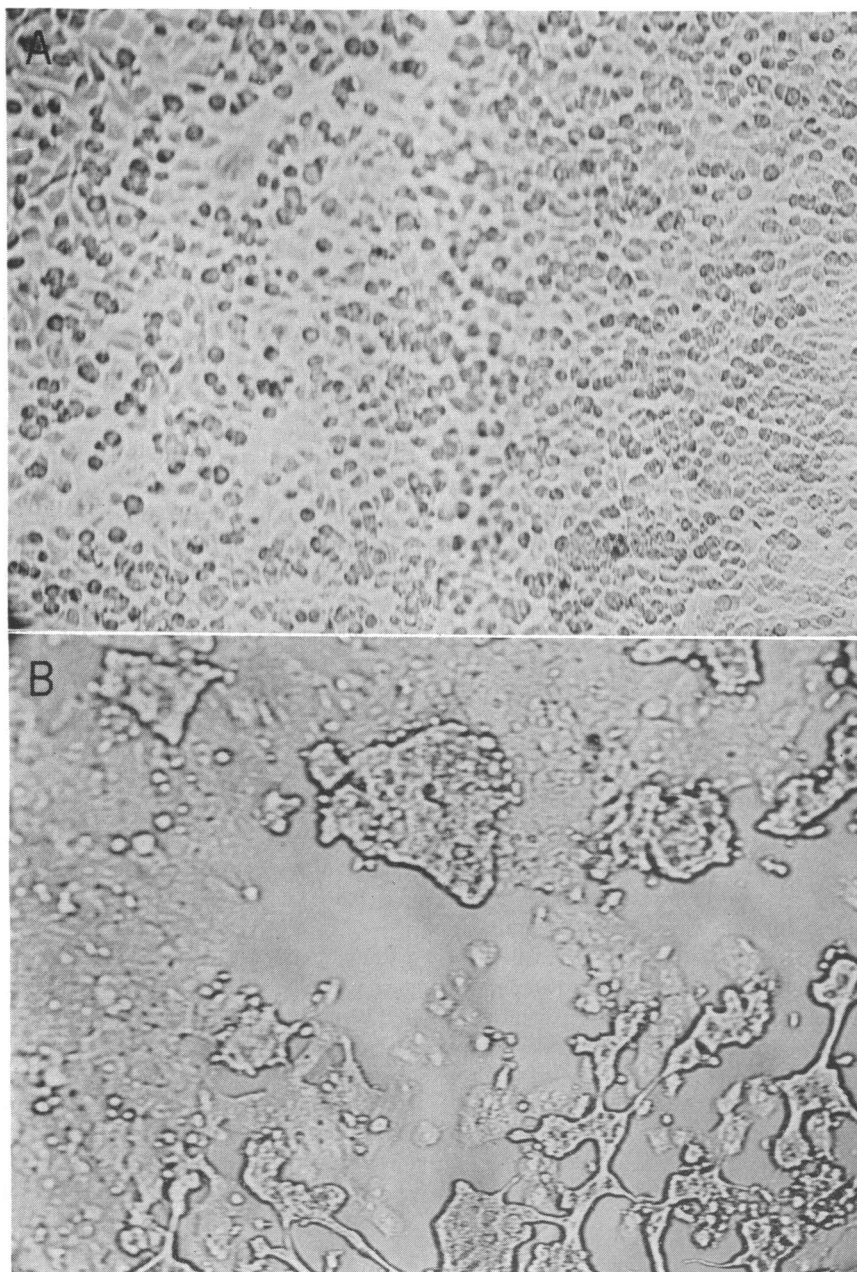


FIG. 2. (A) Photograph of an uninoculated skin-cell culture. 110 $\times$ . (B) Photograph of the cytopathic effect produced by the respiolyticvirus in skin culture. 110 $\times$ .

#### CLINICALLY DISTINGUISHABLE RESPIRATORY ILLNESSES

##### *Influenza*

Both influenza A and B viruses in epidemic or pandemic situations may produce infections and

illnesses which are clinically differentiated and which involve the respiratory tract. In our experience, headache, severe and persistent cough, sore throat, and nasal discharge or obstruction have been the most frequent signs and symptoms of respiratory nature due to influenza

virus infection (Table 5). This, coupled with the high number of cases in the community, the suddenness of onset, and the marked constitutional signs and symptoms out of proportion to duration of illness, is most suggestive of influenzal illnesses.

Herpangina

Herpangina is another respiratory illness of infants and young children in which the diagnosis can be made from findings on physical examination. This illness may be caused by any one of several Coxsackie group A viruses. The disease is

TABLE 5. Symptoms of children with laboratory-confirmed influenza B infection (10)

Symptom	Chief complaint	Symptom
	%	%
Headache.....	43	66
Cough.....	21	75
Sore throat.....	20	43
Nasal discharge or obstruction.....	6	46
Pain or watering of eyes....	1	30
Vomiting or stomach ache.....	9	24
Weakness.....		11
Dizziness.....		9
Hoarseness.....		2
Chills.....		2
Substernal pressure.....		2

most prevalent during the summer months, and the clinical manifestations include fever, anorexia, dysphagia, sore throat, vomiting, abdominal pain, and headache. The characteristic lesions which progress from a papule to a vesicle to a minute ulcer are located in the posterior oropharynx (13). The only disease which must be differentiated from herpangina is herpetic gingivostomatitis due to herpes simplex virus, in which the lesions are on the gums, lips, or tongue.

SUMMARY

This report has summarized the problems encountered in the etiological study of respiratory diseases in infants and children. The relative importance of known viruses as causes of respiratory illnesses has been outlined. Preliminary data are presented on an apparently "new" virus, the "respirolyticvirus," which was recovered from

washings of throat and anal swabs of 64 infants and children during the period of February through April, 1964.

ACKNOWLEDGMENTS

This work was supported by Public Health Service grants AI 6270, NB 5409, AM 8691, and AI-K3-18,291 from the National Institutes of Health.

LITERATURE CITED

1. BEALE, A. J., D. L. McLEOD, W. STACKIW, AND A. J. RHODES. 1958. Isolation of cytopathic agents from the respiratory tract in acute laryngotracheobronchitis. *Brit. Med. J.* **1**:302-303.

2. BEEM, M., F. M. WRIGHT, D. HAMRE, R. EGERER, AND M. OEHME. 1960. Association of the chimpanzee coryza agent with acute respiratory disease in children. *New Engl. J. Med.* **263**:523-530.

3. CHANY, C., P. LEPINE, M. LELONG, L. T. VINH, P. SATGE, AND J. VIRAT. 1958. Severe and fatal pneumonia in infants and young children associated with adenovirus infections. *Am. J. Hyg.* **67**:367-378.

4. CRAMBLETT, H. G. 1960. Croup—present day concept. *Pediatrics* **25**:1071-1076.

5. CRAMBLETT, H. G. 1964. On the etiologic association of viral infection and illness. *Southern Med. J.* **57**:939-942.

6. CRAMBLETT, H. G., H. L. MOFFET, J. P. BLACK, H. K. SHULENBERGER, A. SMITH, AND C. T. COLONNA. 1964. Coxsackie virus infections: clinical and laboratory studies. *J. Pediat.* **64**:406-414.

7. HILLEMANN, M. R., V. V. HAMPARIAN, A. KETTLER, C. M. REILLY, L. MCCLELLAND, D. CORNFELD, AND J. STOKES. 1962. Acute respiratory illnesses among children and adults. *J. Am. Med. Assoc.* **180**:445-453.

8. LERNER, A. M., J. O. KLEIN, J. D. CHERRY, AND M. FINLAND. 1963. New viral exanthems. *New Engl. J. Med.* **269**:678-685, 736-740.

9. McLEAN, D. M., R. D. BACH, R. P. B. LARKE, AND G. A. McNAUGHTON. 1963. Myxoviruses associated with acute laryngotracheobronchitis in Toronto, 1962-1963. *Can. Med. Assoc. J.* **89**:1257-1259.

10. MOFFET, H. L., H. G. CRAMBLETT, G. K. MIDDLETON, JR., J. P. BLACK, H. K. SHULENBERGER, AND A. M. YONGUE. 1962. Outbreak of influenza B in a children's home. *J. Am. Med. Assoc.* **182**:834-838.

11. MOFFET, H. L., AND H. G. CRAMBLETT. 1962.

- Viral isolations and illnesses in young infants attending a well baby clinic. *New Engl. J. Med.* **267**:1213-1218.
12. MOFFET, H. L., H. G. CRAMBLETT, AND A. SMITH. 1964. Group A streptococcal infections in a children's home. II. Clinical and epidemiological patterns of illness. *Pediatrics* **33**:11-17.
  13. PARROTT, R. H., AND H. G. CRAMBLETT. 1957. Non-bacterial infections affecting the nasopharynx. *Pediat. Clin. North Am.* **4**:115-138.
  14. PARROTT, R. H., H. W. KIM, A. J. VARGOSKO, AND R. M. CHANOCK. 1962. Serious respiratory tract illness as a result of Asian influenza and influenza B infections in children. *J. Pediat.* **61**:205-213.
  15. PARROTT, R. H., A. J. VARGOSKO, H. W. KIM, J. A. BELL, AND R. M. CHANOCK. 1962. Acute respiratory diseases of viral etiology. III. Myxoviruses: parainfluenza. *Am. J. Public Health* **52**:907-917.
  16. PARROTT, R. H. 1963. Viral respiratory tract illnesses in children. *Bull. N.Y. Acad. Med.* **39**:629-648.
  17. PEREIRA, M. S., AND O. D. FISHER. 1960. An outbreak of acute laryngotracheobronchitis associated with parainfluenza-2 virus. *Lancet* **2**:790-791.
  18. RABE, E. F. 1948. Infectious croup. I. Etiology. *Pediatrics* **2**:255-265.
  19. REILLY, C. M., S. M. HOCH, J. STOKES, JR., L. McCLELLAND, V. V. HAMPARIAN, A. KETLER, AND M. R. HILLEMAN. 1962. Clinical and laboratory findings in cases of respiratory illness caused by coryzaviruses. *Ann. Intern. Med.* **57**:515-525.
  20. UTZ, J. P., J. A. KASEL, H. G. CRAMBLETT, C. F. SZWED, AND R. H. PARROTT. 1957. Clinical and laboratory studies of mumps. I. Laboratory diagnosis by tissue-culture technics. *New Engl. J. Med.* **257**:497-502.
  21. VAN DER VEEN, J. 1963. The role of adenoviruses in respiratory disease. *Am. Rev. Respirat. Diseases* **88**:167-180.
  22. WULFF, H., P. KIDD, AND H. A. WENNER. 1964. Etiology of respiratory infections: further studies during infancy and childhood. *Pediatrics* **33**:30-44.